Ovarian immature teratoma; report of four cases

FATEN LIMAIEM1, ASMA SASSI1, SAADIA BOURAOUT1
1University of Tunis El Manar, Tunis Faculty Of Medicine, 1007, Tunisia

ABSTRACT
Immature teratomas are rare malignant germ cell neoplasms accounting for less than 1% of all ovarian tumors. The aim of this study was to provide an updated overview on clinicopathological features, treatment and outcome of immature teratoma of the ovary. Our study group included four women aged between 20 and 49 years (mean = 29.5 years). The presenting clinical symptoms were dominated by pelvic pain (n=4), followed by perception of a pelvic mass (n=2) and altered general health (n=1). All patients underwent surgical resection of the tumor. Histopathological examination of the surgical specimen established the diagnosis of high grade immature teratomas in all cases. Local recurrence of the tumor occurred in one case and one patient had hepatic metastases. The other two patients are still being followed-up. The majority of patients diagnosed with an immature teratoma are cured of their disease. However, grade 2 or 3 tumors are associated with a greater chance of recurrence that can be fatal, predominantly within 2 years of diagnosis.

Key words: immature teratoma, ovary, germ cell tumor

INTRODUCTION
Immature teratomas are rare malignant germ cell neoplasms accounting for less than 1% of all ovarian tumors and 20% of malignant ovarian germ cell tumors. They contain elements resembling embryonic tissues derived from all three germ layers with immature neuroepithelium used to grade these tumors. Due to their rarity, data on immature ovarian teratomas are limited. Most population-based studies have examined malignant ovarian germ cell tumors as a group, while those studies focusing on immature teratomas have consisted of small, retrospective single-institution series. In this paper, we report four cases of ovarian immature teratomas. Our aim was to analyze their clinicopathological features, treatment and outcomes.

METHODS
We undertook a retrospective study of four patients who were operated on for immature ovarian teratoma at the gynaecology department of Mongi Slim hospital of Tunisia between June 2000 and December 2013. The cases were retrieved from the files of the registry of gynaecology department of the same hospital. Medical records were scrutinized for epidemiologic characteristics, initial manifestations of the disease, methods of diagnosis, laboratory findings, surgical or palliative therapy and overall morbidity and mortality. Diagnosis of immature teratoma was based upon histopathological findings. All patients underwent imaging evaluation during the preoperative period. All specimens were surgically obtained. Tissues were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin and sections were prepared for routine light microscopy after staining with haematoxylin and eosin. Patient confidentiality was maintained. Tumors were staged according to the grading system of Thurlbeck and Scully as well as to the two-tiered grading system (O’Connor and Norris).

RESULTS
Clinical findings
Our study group included four female patients between 20 and 49 years of age (mean = 29.5 years). Two patients presented with co-morbidities namely asthma (n=1) and tuberculosis (n=1). The presenting clinical symptoms were dominated by pelvic pain (n=4), followed by perception of a pelvic mass (n=2) and altered general health (n=1).

Biological tests
Preoperative serum Alpha-fetoprotein (AFP) levels were performed in three cases. They were elevated in one case (> 10 ng/ml) and within normal range in two cases (< 10 ng/ml).

Radiological findings and localization of immature teratomas
Diagnostic imaging techniques included abdominal
ultrasonography in all cases and CT scan in two cases (cases 2 and 3). The tumor involved the right ovary in two cases (cases 2 and 3) and the left ovary in two cases (cases 1 and 4). Ultrasonography revealed a heterogeneous, partially solid lesion, with scattered calcifications in three cases. At CT scan, immature teratomas had a large, irregular solid component containing coarse calcifications.

**Treatment**
All patients underwent surgical treatment including total hysterectomy with bilateral salpingo-oophorectomy and appendectomy (n=1) and salpingo-oophorectomy (n=3). Postoperatively, the four patients received adjuvant chemotherapy including four cycles of BEP (bleomycin, etoposide, and cisplatin).

**Pathologic findings**
In our series, ovarian immature teratomas ranged in size from 19 to 32 cm (mean = 23.5 cm). The cut section was variegated with solid and cystic areas. The tumor was predominantly solid with interspersed cysts in one case (case 4) (Fig. 1B), predominantly cystic in one case (case 3) and semi-solid mid cystic in two cases (cases 1 and 2). The cystic component of the tumor was filled sebaceous material, hair (cases 1, 2, and 3) and mucin (case 2). Bone was identified in three cases (cases 2, 3, and 4). Hemorrhage was found in three cases (cases 2, 3, and 4) and necrosis in one case (case 2). Microscopically, most areas of the tumor were composed of abundant mature glial tissue along with skin and adnexal structures, glandular elements, mature and immature cartilage (Fig. 1C). Focal areas showed primitive neuroepithelium in the form of primitive neural tubes and rosettes (Fig. 1D).

**Staging of immature teratomas**
Based on the relative amounts of immature neuroectodermal component, immature teratomas of our series were graded according to the grading system of Thurlbeck and Scully (Table 2) as grade 2 in three cases and as grade 3 in one case. According to the two-tiered grading system (Table 2) of immature teratomas, the four tumors of our series were classified as high-grade tumors.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Tumor size (cm)/ location</th>
<th>Grade</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>19/ Left ovary</td>
<td>2 (high grade)</td>
<td>Pelvic pain and mass.</td>
<td>Left salpingo-oophorectomy</td>
<td>Local recurrence of the tumour six months postoperatively</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>24/ Right ovary</td>
<td>2 (high grade)</td>
<td>Pelvic pain Altered general health</td>
<td>Right salpingo-oophorectomy</td>
<td>No recurrence No metastases Still being followed-up</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>32/ Right ovary</td>
<td>3 (high grade)</td>
<td>Pelvic pain and mass.</td>
<td>Total hysterectomy, bilateral salpingo-oophorectomy and appendectomy</td>
<td>Liver metastases</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>19/ Left ovary</td>
<td>2 (high grade)</td>
<td>Pelvic pain</td>
<td>Right salpingo-oophorectomy</td>
<td>No recurrence No metastases Still being followed-up</td>
</tr>
</tbody>
</table>

**Operative morbidity and postoperative complications**
Postoperative course was uneventful in all cases.

**Follow-up and evolution**
The mean follow-up period of our patients was 15 months (range: 3 - 36 months). Local recurrence of the tumor occurred in one case (case 1). In the control examination, CT scan revealed four hypodense heterogeneous lesions in liver segments III, IV, VII and VI (case 3) which were in favor of metastases (Fig. 1A). The patient underwent surgical excision of the liver lesions. Histological examination confirmed the diagnosis of hepatic metastasis of immature teratoma. The other two patients are still being followed-up (cases 2 and 4).

**DISCUSSION**
Immature teratoma is defined as a malignant germ cell neoplasm containing patterns of differentiation that recapitulate that seen in embryonic and fetal tissues. Like other malignant germ cell tumors, immature teratomas predominate in the second and third decades and fewer than 10% are seen in women older than age 30.2 In our series, the patients were aged between 20 and 49 years (mean = 29.5 years). The presenting symptoms of malignant immature teratoma include abdominal pain and distension. Sixteen percent of patients experience adnexal torsion, 1-2% ruptures and 1% infection.
In our series, the presenting clinical symptoms were dominated by pelvic pain (n=4), followed by perception of a pelvic mass (n=2) and altered general health (n=1). Traditionally, immature teratoma is not considered to be associated with raised AFP or ßHCG unless it is part of a mixed germ cell tumor. In our series, preoperative AFP levels were performed in three cases. They were elevated in one case (> 10 ng/ml) and within normal range in two cases (< 10 ng/ml). The ultrasonography appearances of immature teratoma are nonspecific, although the tumors are typically heterogeneous, partially solid lesions, usually with scattered calcifications. At CT and MR imaging, immature teratomas characteristically have a large, irregular solid component containing coarse calcifications. Small foci of fat help identify these tumors. Grossly, immature teratoma is typically unilateral, large, predominantly solid, fleshy, grey-tan in color and may contain cysts, haemorrhage and necrosis. Histologically, variable amounts of embryonal-type tissues, mostly in the form of neuroectodermal tubules and rosettes but sometimes with a conspicuous component of cellular mitotically active glia, are admixed with ectodermal and endodermal elements, with varying degrees of maturation. The tubules are lined by overlapping, hyperchromatic cells with numerous mitoses and may be pigmented. Immature cartilage, adipose tissue, bone and skeletal muscle are often present. Endodermal structures including hepatic tissue, immature gastrointestinal tract and embryonic renal tissue are less common. The most common primitive component of immature teratoma is in the form of embryoid bodies constituted by yolk sac epithelium and germ disk whose epithelium resembles that of embryonal carcinoma. A conspicuous reactive vascular proliferation may be seen in immature teratomas. Based on the relative amounts of immature neuroectodermal component, immature teratomas have been graded from one to three, but a two-tiered (low- and high-grade) system is now more commonly used. In a follow-up report, O'Connor and Norris proposed a two-grade system, in which any tumor with immature elements exceeding one low-power field per slide was classified as a high-grade tumor, without separating grades 2 and 3. This approach is supported by both the cut-off point for aggressive behaviour (grade 2) and the traditional clinical management guidelines for stage I immature teratomas, which recommended chemotherapy for both grades 2 and 3. Thus, the critical decision is determining the extent of immature teratomatous

**Table 2.** Grading of ovarian immature teratomas using a three-tiered grading system.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histological criteria</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>Tumors with rare foci of immature neuroepithelial tissue that occupy &lt; 1 low power field (40 x) in any slide (low grade).</td>
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<tr>
<td>Grade 2</td>
<td>Tumors with similar elements, occupying 1-3 low power fields (40 x) in any slide (high grade).</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Tumors with large amount of immature neuroepithelial tissue occupying &gt; 3 low power fields (40 x) in any slide (high grade).</td>
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elements in the tumor in question, and these tumors can thus be classified as low (grade 1) or high grade (grades 2-3) based on management. An important pitfall in this assessment is normal neuroepithelium, which is typically found in mature cystic teratomas and should not be confused with immature elements.\textsuperscript{7} Immunohistochemically, the intestinal and immature neural elements are SALL4 positive.\textsuperscript{8} SOX2 and glypican 3 are positive in the neuroepithelium. Alpha-fetoprotein may stain immature gastrointestinal-type glands.\textsuperscript{8} Treatment consists of unilateral salpingo-oophorectomy with wide sampling of peritoneal implants. If the tumor if confined to the ovary and grade 1, no further therapy is needed. However, chemotherapy (including bleomycin, etoposide, and platinum) is recommended for higher grade and stage disease.\textsuperscript{9} Treatment with surgery followed by systemic chemotherapy can achieve remission and cure in over 90\% of cases.\textsuperscript{10,11} There is no evidence that contralateral oophorectomy, hysterectomy, or radiation therapy will improve survival. Although chemotherapy has improved prognosis of immature teratomas, stage and grade of the primary tumor and metastases remain important predictive factors. In approximately one-third of cases, innumerable miliary nodules of mature glia occur in the peritoneum (gliomatosis peritonei) and abdominal lymph nodes, but the prognosis remains favourable.\textsuperscript{12}

**CONCLUSION**

In summary, this study reflects the epidemiologic trends in the presentation, management, and outcomes of women with immature ovarian teratoma. Future research should be directed to decreasing the toxicities of treatment and to further improve the already high survivals. It is necessary to identify newer drugs with less serious toxicities for treating high-risk disease. Novel molecular biomarkers are needed to help identify those at risk for persistent or recurrent disease and for selecting potential targeted therapies.

**REFERENCES**